



Advancing Transfusion and  
Cellular Therapies Worldwide

**ASSOCIATION BULLETIN**  
**#06-08**

Date: December 14, 2006  
To: AABB Members  
From: D. Michael Strong, PhD, MT(ASCP), BCLD(ABB) – President  
Karen Shoos Lipton, JD – Chief Executive Officer  
Re: Information Concerning Implementation of a Licensed Test for Antibodies  
to *Trypanosoma cruzi*

**Summary**

This bulletin contains information to consider in determining 1) whether to implement a licensed test for antibodies to *Trypanosoma cruzi* (the agent of Chagas' disease), 2) the time frame for such implementation, and 3) medical information relevant to donor and recipient follow-up. Recommendations for facilities that implement a licensed test for *T. cruzi* antibodies address the following:

- Quarantine, including prior in-date components and consignee notification.
- Look-back and recipient testing.
- Release of components from autologous donors with repeat-reactive test results.
- Donor deferral, notification, and confirmatory testing.
- Referral of donor for medical evaluation.

FDA recently granted a license to one manufacturer of a *T. cruzi* antibody test kit. In addition to screening donors of whole blood, this test is intended for use in screening plasma and serum samples from cell, organ and tissue donors (heart-beating). At this time, the test is not approved for use on specimens from cadaveric donors (non-heart-beating).

**Background Regarding the Agent**

Chagas' disease is caused by the protozoan parasite, *T. cruzi*. The parasite is found only in the continental Americas, usually in Latin America. The agent has rarely been reported to cause natural (autochthonous) human infection in the United States (US). The presence of the agent in the US and Canada, however, is increasing as a result of the immigration of infected individuals from areas where the parasite is endemic.

Natural infections are transmitted mainly when the feces of blood-sucking bugs (triatomine bugs commonly referred to as kissing or reduviid bugs) that harbor the

infection are rubbed into a bug bite, other wound, or directly into the eyes or mucous membranes. Other primary forms of transmission include congenital transmission (mother to fetus), organ transplantation, blood transfusion and rarely by ingestion of contaminated foods. Acute, vector-borne infections are mostly mild, but then persist throughout life, usually without symptoms.

The lifetime risk of severe heart or intestinal problems in infected individuals averages about 30% (range of 10-40%, depending on a variety of factors) and usually occur many years after the initial infection. During the chronic stage, most persons who harbor the parasite are asymptomatic and unaware of their infections. In contrast, acute infection in patients with compromised immune systems (eg, from cancer therapy or organ transplantation) can be very serious.

Treatment options are limited, but are most effective early in the infection. The Centers for Disease Control and Prevention (CDC) is currently reviewing the available clinical experience regarding the efficacy of treatment during various stages of infection and is expected to make additional information and recommendations available in the future.

It is estimated that at least 11 million persons carry the parasite chronically in Mexico and in Central and South America and thus serve as a source of infection in the transfusion setting. Among infected persons, up to 45,000 fatalities may occur annually. Some experts estimate that there may be as many as 100,000 legal immigrants in the US and Canada who are unknowingly infected with *T. cruzi*. Published studies estimate that the rate of seropositive blood donors in the US ranges from 1 in 5400 to 1 in 25,000, depending on where the studies were conducted. However, ongoing investigational studies suggest that these rates have increased and are as high as 1 in 2000 in the Los Angeles metropolitan area. Transfusion transmission in endemic areas has been a major public health concern. Many countries in which *T. cruzi* infection is considered endemic screen blood donors for the presence of antibody. Therefore, in response to changes in donor demographics, blood screening in the US is being considered.

In the US and Canada, only seven cases of transfusion-transmitted *T. cruzi* and five cases of infection from organ transplantation have been documented. However, it is well accepted that many other cases have occurred but have not been recognized. Transmission in an immunocompetent patient is not likely to be apparent, and in many cases, even if symptoms appear, infection is not likely to be recognized. In large part, this is because of the nonspecific nature of symptoms in transfusion recipients and the unfamiliarity of physicians with *T. cruzi* infection and Chagas' disease.

Blood centers having high to moderate numbers of donors from countries where infection is endemic have questioned donors about birth and/or residence of six months or longer in such a country. These centers have identified up to 14% of donors responding "yes" to such a question; however, when donors who responded "no" to the same question were subsequently tested, an antibody confirmed-positive donor who did not understand the question was identified. In additional studies, antibody confirmed-positive donors were identified who lacked any apparent risk factors. When confirmed-positive donors were

questioned further about time away from the area where infection was endemic, most donors stated that they had been in the US for many years (mean of 17 years). Therefore, questions to identify risk in the US have not been implemented. Instead the blood banking community has been waiting for the availability of an appropriate test for blood donor screening.

Studies have also looked at the efficiency of transmission from *T. cruzi* antibody-positive individuals. Because of the characteristics of the parasite, the most efficient route of blood-borne transmission is either via whole blood or platelets. Focusing on these components, published look-back studies in the US have identified one infected recipient among four platelet recipients studied. In Mexico, four infected whole blood or platelet recipients were identified among nine studied. Thus, a total of five positive recipients have been identified among the 13 studied (38.5%). This figure is consistent with the literature from Latin America on rates of blood-borne transmission.

### **Current Status of Blood Donor Screening**

FDA recently granted a license to one manufacturer of a *T. cruzi* antibody test kit (Ortho *T. cruzi* ELISA Test System, Ortho-Clinical Diagnostics, Raritan, NJ). Abbott Laboratories has also stated publicly that it has plans to open an investigational new drug trial to qualify its test, but it is likely that only one licensed test will be available for the foreseeable future.

The Ortho *T. cruzi* antibody test is based on the capture of *T. cruzi* antibody in a sample of the donor's serum or plasma using purified *T. cruzi* epimastigote lysate. In addition to screening donors of whole blood, this test is intended for use in screening plasma and serum samples from cell, organ and tissue donors (heart-beating). At this time, the test is not approved for use on specimens from cadaveric donors (non-heart-beating).

In response to the availability of a suitable licensed test and changes in donor demographics, multiple large blood collectors and providers are expected to implement the licensed test by February 2007. Each facility should consider whether to implement a licensed test as well as the time frame for such implementation. In considering implementation, facilities may be aided by estimation of the percent population in the collection area that has emigrated from Mexico and Central and South America (excluding the Caribbean islands where infection has not been reported). However, without specific data on *T. cruzi* seroprevalence, accurate risk estimates for an individual blood establishment should be considered an unknown. Cases of transfusion-transmitted Chagas' disease have occurred outside of those areas of the US and Canada considered to be of high risk (ie, a state with demonstrated seroprevalence – namely, Florida and those that border Mexico).

AABB is investigating a web-based tracking system for Chagas' similar to that implemented in 2006 for West Nile virus reactive/confirmed positive donations to include donor test results and donor demographics (as available). Facilities that do not immediately implement the licensed test can benefit from the data reported by those institutions that have implemented testing.

Most blood collectors that implement testing will test all donated allogeneic and autologous units, as is done for human immunodeficiency virus, hepatitis B virus, hepatitis C virus, etc. It is expected that FDA will recommend testing of all donations (as has been required for all other major transfusion-transmitted agents) when a guidance document on issues related to *T. cruzi* antibody donor testing and component management is released. It should be noted that FDA stated publicly at the September 12, 2002 Blood Products Advisory Committee (BPAC) meeting that testing would be recommended following the availability of an appropriate test for blood donor screening. This position was unanimously supported by the BPAC.

Although, as stated, blood centers that implement testing will test all donations, other approaches (such as testing each donor once and recording the *T. cruzi* antibody status) may achieve the same level of blood component safety. Before alternate test approaches can be implemented, however, the following requirements will need to be met: 1) validated computer systems to maintain donor information, 2) qualification regarding comparable sensitivity and specificity to testing all donations, and 3) FDA approval that these alternate test approaches are acceptable.

### **Recommended Actions for Donors and Donations Testing Repeat Reactive by a Licensed Test for *T. cruzi* Antibody**

#### *Components*

- Components from repeat-reactive index donations should be quarantined and destroyed or used for research following appropriate labeling. Prior in-date components from a donor who later has been shown to be repeat reactive by a licensed test for *T. cruzi* antibody should be quarantined and withdrawn with a notification to all consignees of distributed components (in addition, see below). In the past, FDA has required that these actions occur within three calendar days except for plasma intended for further manufacturing (see below).
- Look-back (recipient tracing and testing) should occur for transfused components of all prior donations from confirmed-positive donors (defined below). This look-back should occur using the same model currently used for anti-HCV (ie, for as long as electronic or other readily retrievable records exist). Although laboratory studies have shown that *T. cruzi* is killed by freezing and thus the risk of transmission of *T. cruzi* from frozen plasma or other frozen components is considered very low, the above actions should also occur for frozen components because the available data are limited. Recipients of previous components from confirmed-positive donors should be tested for the presence of *T. cruzi* antibodies.
- Components from donations from autologous donors that test repeat reactive by a licensed test for *T. cruzi* antibody may be released to hospitals with approval of the autologous donor's referring physician. Collection/testing facilities will provide the results of confirmatory testing as available.
- At the present time, it is expected that source plasma donations and recovered plasma intended for further manufacture will not require *T. cruzi* antibody screening. Studies

have shown that current methods used in further manufacturing have demonstrated effective parasite inactivation.

- Inventory testing (ie, testing of distributed or in-house inventory) is not recommended at this time but consideration of the risks should be undertaken by each blood establishment.

#### *Donors*

- All donors whose donations test repeat reactive by the licensed test for *T. cruzi* antibody should be indefinitely deferred and notified of their deferral. Confirmatory testing, defined as testing by a second test of a different format, is strongly recommended for such donors with permanent deferrals applied to those who test confirmed-positive.
- Confirmatory testing by radioimmunoprecipitation assay (RIPA), indirect immune fluorescence assay (IFA), or other diagnostic test for *T. cruzi* antibody will be available from reference laboratories in the US. RIPA, although not licensed for this use, has been used for all US-based clinical studies (using methods described by L.V. Kirchhoff) and is considered the most sensitive available test, although its sensitivity is not 100%. Ortho Clinical Diagnostics is currently working with Quest Diagnostics in Chantilly, VA to make RIPA testing available to blood centers at that location.
- Because no licensed confirmatory test is available there is no donor reentry protocol that can be recommended for those donors who have tested falsely positive. AABB will work with FDA to validate donor reentry algorithms even in the absence of a licensed confirmatory/supplemental test for *T. cruzi* antibody.
- If confirmatory testing cannot be performed, institutions should defer and notify donors of such deferral on the basis of repeat-reactive results of the licensed screening test.
- Donor follow-up studies may be useful to 1) determine the specificity of the index reactive screening results, 2) monitor for antibody progression in confirmatory negative/indeterminate individuals, and 3) serve as a means of collecting data that may be used to qualify algorithms for donor reentry.
- Testing facilities may wish to consider testing donors who are reactive by the licensed *T. cruzi* antibody but who do not confirm as positive, or have no apparent exposure to *T. cruzi*, for antibodies to *Leishmania*. Antibodies from *T. cruzi* and *Leishmania* demonstrate some cross-reactivity and it is possible that US blood donors may have been exposed to *Leishmania*. Commercial reference laboratories routinely offer diagnostic testing for *Leishmania*.
- All donors who test confirmed positive for *T. cruzi* antibodies should be referred to a physician knowledgeable about the evaluation and treatment of *T. cruzi* infection. It may also be useful to refer all confirmed-positive donors to their state and local health departments or other appropriate community resource.
- CDC is currently working on health recommendations that will be communicated in the future. Current information is available at the CDC Web site at <http://www.cdc.gov/ncidod/dpd/parasites/chagasdisease/default.htm> .

- Testing of recipients identified by look-back, family members of confirmed-positive donors and others who have risk of infection may be referred to CDC, a local reference laboratory that performs *T. cruzi* diagnostic testing, or the blood center. Although the licensed test does not have a diagnostic claim relative to the diagnosis of Chagas' disease or *T. cruzi* infection in an individual, the licensed test for antibody detection has been shown to have suitable performance characteristics for blood donor screening and as such may be useful in testing of the above individuals.

#### *Other*

- The *Circular of Information for the Use of Human Blood and Blood Components* may be updated stating the use of the licensed test and that associated components from such tested donations have tested nonreactive. The Circular of Information Task Force will provide appropriate language.
- The Blood Bank/Transfusion Services Standards Program Unit is currently evaluating this issue and is considering whether an interim standard regarding implementation of a Chagas' test to *Standards for Blood Banks and Transfusion Services, 24<sup>th</sup> Edition*, is necessary.

#### **Bibliography**

Chang CD, Cheng KY, Jiang LX, et al. Evaluation of a prototype *Trypanosoma cruzi* antibody assay with recombinant antigens on a fully automated chemiluminescence analyzer for blood donor screening. *Transfusion* 2006;46:1737-44.

Leiby DA, Fucci MH, Stumpf RJ. *Trypanosoma cruzi* in a low- to moderate-risk donor population: Seroprevalence and possible congenital transmission. *Transfusion* 1999;39:10-15.

Leiby DA, Herron RM, Read EJ, et al. *Trypanosoma cruzi* in Los Angeles and Miami blood donors: Impact of evolving donor demographics and seroprevalence and implications for transfusion transmission. *Transfusion* 2002;42:549-55

Leiby DA, Lenes BA, Tibbals MA, Tames-Olmedo MT. Prospective evaluation of a patient with *Trypanosoma cruzi* infection transmitted by transfusion. *N Engl J Med* 1999;341:1237-9.

Leiby DA, Rentas FJ, Nelson, et al. Evidence of *Trypanosoma cruzi* infection (Chagas' disease) among patients undergoing cardiac surgery. *Circulation* 2000;102:2978-82.

Leiby DA, Wendel S, Takaoka DT, et al. Serologic testing for *Trypanosoma cruzi*: Comparison of radioimmunoprecipitation assay with commercially available indirect immunofluorescence assay, indirect hemagglutination assay, and enzyme-linked immunosorbent assay kits. *J Clin Microbiol* 2000;38:639-642.

Kirchhoff LV. American trypanosomiasis (Chagas' disease) -- a tropical disease now in the United States. *N Engl J Med* 1993;329:639-44.

Kirchhoff LV. Changing epidemiology and approaches to therapy for Chagas' disease. *Curr Infect Dis Rep* 2003;5:59-65.

Kirchhoff LV, Gam AA, Gusmao RD, et al. Increased specificity of serodiagnosis of Chagas' disease by detection of antibody to the 72- and 90-kilodalton glycoproteins of *Trypanosoma cruzi*. *J Infect Dis* 1987;155:561-4.

Kirchhoff LV, Paredes P, Lomeli-Guerrero A, et al. Transfusion-associated Chagas' disease (American trypanosomiasis) in Mexico; implications for transfusion medicine in the United States. *Transfusion* 2006;46:298-304.

Mascola L, Kubak B, Radhakrishna S, et al. Chagas disease after organ transplantation – Los Angeles, California, 2006. *MMWR Morb Mortal Wkly Rep* 2006;55:789-800.